

Ophthalmological and otological problems in Turner syndrome

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Abstract. Ocular abnormalities are common in Turner syndrome (TS). They include epicanthal folds, ptosis, and hypertelorism. Red–green color deficiency is also more common in TS. Non-familial strabismus and hyperopia occur in 25–25% of TS children. To prevent visual loss, children with TS should be evaluated by a pediatric ophthalmologist at 12–18 months of age. Hearing problems and ear malfunctions are also common in TS and correlate with the karyotype. As a result of the frequent otitis media, conductive hearing loss is common in girls with TS. Sensorineural hearing loss is also common and may occur as early as 6 years of age. It is usually manifest by a sensorineural dip in the 1.5–2 kHz region and/or high frequency loss (above 8 kHz). By middle age, the hearing deficit often has serious professional and social consequences and a quarter of the TS women will require hearing aids. Otitis media has to be treated aggressively. Currently the only possible intervention to reduce hearing loss in women with TS remains the assiduous treatment of ENT problems in childhood. Growth hormone treatment as well as estrogen treatment has no effect on the progression. © 2006 Published by Elsevier B.V.

Keywords: Turner syndrome; Otologic; Sensorineural hearing loss; Otitis media; Ophthalmologic; Strabismus; Amblyopia; Glaucoma; Pseudotumor cerebri

1. Introduction

Disorders of the eye and the ear are frequent complaints in patients with TS. Particularly, impairment of sensorineural hearing in older TS is often extremely incapacitating for these patients. This conference will address what is known about eye and ear disease in TS and will formulate new recommendations. In the most recent guidelines for the diagnosis and

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0531-5131/ © 2006 Published by Elsevier B.V.

doi:[10.1016/j.ics.2006.06.021](https://doi.org/10.1016/j.ics.2006.06.021)

management of TS published in 2001 [1] the authors state the common ophthalmologic and otologic abnormalities in girls with Turner syndrome.

1.1. Vision

Strabismus, amblyopia, and ptosis are common in TS. Ophthalmological evaluation should be part of the regular physical examination, with referral when appropriate.

1.2. Hearing

Conductive and sensorineural hearing losses are common in girls with TS. The outer, middle and inner ears are all affected; and hearing problems and ear malformations correlate with the karyotype.

1.2.1. Outer ear

Mild malformations of the outer ear and low set ears occur in 30–50% of individuals with TS.

1.2.2. Middle ear

Otitis media is extremely common in girls with TS and may progress to mastoiditis and/or cholesteatoma formation. It occurs particularly between 1 and 6 years of age with a maximum incidence (more than 60%) at 3 years of age. The cause is still unknown, but growth retardation of the temporal bone with altered position of the Eustachian tube may be important. Aggressive treatment of otitis media is appropriate, and insertion of ventilation tubes should be considered. Careful follow-up is important. Patients with chronic middle ear problems should be operated without delay to prevent sequelae. Short girls with extensive otitis media problems should be referred to an endocrinologist if TS has not been previously diagnosed.

1.2.3. Inner ear

The majority (50–90%) of women with TS have sensorineural hearing loss (SNHL), manifested by a sensorineural dip in the 1.5–2 kHz region, sensorineural high frequency loss, or all of these. The sensorineural dip can occur as early as 6 years of age and occasionally leads to hearing problems in later life, which may have serious social consequences. Hearing aids are frequently necessary. If only a sensorineural dip is present, follow-up should occur every 3–5 years. Otological follow-up assessments should be conducted every 10 years in patients who do not have hearing problems and whose karyotype is a low risk indicator for otitis media or a sensorineural dip (i.e. 45,X or 46X,I (Xq0)).

In the National Cooperative Growth Study (NCGS) [2], a postmarketing surveillance registry established in 1985 to monitor the safety and efficacy of biosynthetic growth hormone in patients treated in North America, a large database for TS has been established. Data were collected for 955 girls with TS. In this well characterized study group, which was enrolled from 1986 to 2000, the development of chronic otitis media and progressive hearing loss has been described. In the NCGS study a cohort of 515 (54%) patients had a

history of frequent otitis media; cholesteatoma was reported in 14 (1%) of the patients. Of those patients with a history of frequent otitis media, 215 (42%) underwent a hearing evaluation and 112 (52%) reported hearing loss. Hearing loss was reported as mild (57%), moderate (27%) or severe (10%). Conductive hearing loss was most common (72%) followed by sensorineural abnormalities (18%). Over the years hearing tests actually decreased in frequency, despite the well-known risk of hearing loss in patients with TS. These data stress the importance of increased educational efforts to recognize and treat comorbidities in TS early and effectively.

2. Ophthalmologic abnormalities

Ocular abnormalities are common in this syndrome and are found in up to 22% of patients with TS (Gorlin) [3].

2.1. Anterior segment abnormalities [4,5]

Anterior segment abnormalities include amblyopia 42%, strabismus 33–38%, blue sclerae 29%, ptosis 16–29%, hypertelorism 10%, epicanthus 10–46%, hypermetropia 42%, red–green color deficiency 10%, congenital cataract 4–8%, corneal nebulae, uveitis and congenital glaucoma. Lloyd et al. [5] describe particularly congenital glaucoma and other forms of anterior segment dysgenesis in patients with mosaic TS while other reports do not support karyotype–phenotype associations.

2.2. Posterior segment abnormalities

Posterior segment abnormalities include neovascularization, retinal detachment, and papilledema as part of pseudotumor cerebri.

In several patients, unilateral retinal neovascularization was described. In most patients cases the infants had received oxygen postnatally [6]. In TS, therefore, early fundus examination is recommended to identify possible development of abnormal retinal vessels and to prevent poor visual outcome in affected the eye with successful, early retinal photocoagulation. Of particular concern are retinal changes mimicking diabetic retinopathy in GH-treated patients with no evidence of diabetes mellitus. In one patient with TS (45X/46Xmar, SRY+) within 22 months of GH therapy unilateral neovascularization developed. This very rare complication may represent acceleration of unrecognized pre-existing retinopathy. Hyperglycemia is thus not mandatory for initiating retinopathy although it may alter its course [7]. Baseline and periodic fundoscopic evaluation should therefore be performed in all patients receiving GH, not just in TS patients. In addition, benign pseudotumor cerebri with papilledema may develop in Turner patients treated with growth hormone. There should be a low threshold for referral to ophthalmologists for these patients.

3. Ear and hearing

The association of TS with recurrent otitis media (OM) and sensorineural hearing loss is well documented since the first study by Lindsten in 1963, [8]. In 1969, Anderson et al. [9]

presented audiometric and otologic data from 19 clinical cases of TS in the first large survey of the prevalence of ear disease in TS. Nearly 70% of these patients had a history of middle ear infections, and 64% had documented sensorineural hearing loss (SNHL) or mixed hearing loss. More than half of the patients reported not only recurrent episodes but also spontaneous perforations, the need for surgical treatment or both. In our series [10], complete system reviews were recorded for more than 80% of the patients. Of these almost 75% had undergone tonsillectomy and adenoidectomy because of recurrent otitis or had both procedures performed. Of these, 5 patients had also undergone mastoid surgery. In a recent review on otologic disease, Dhooge et al. [11] present a synoptical overview of the types of hearing loss in TS (Tables 1–3).

3.1. Otitis media (OM)

Excessive otitis media in TS is evident when there is history of myringotomy and tube placement or tympanomastoid surgery, or a medical record documentation of impaired conductive hearing, retraction pocket or cholesteatoma [12]. The conductive losses appear to be secondary to OM and poor Eustachian tube function rather than to any congenital ossicular anomaly. The cause of otitis does not appear to be related to a specific or generalized immunologic dysfunction. Other infections, as well as other disorders of the mucous membranes are not reported to occur with increased frequency in TS. Instead, the frequent occurrence of otitis may be the consequence of abnormalities in growth of the cranial base in TS. Cephalometry has documented that both structural growth of the temporal bone and growth of the condylar cartilage and spheno-occipital synchondrosis are abnormal. The result is that the final development of the facial skeleton reaches a level only corresponding to that of an 11-year-old girl, whereas that of the posterior portion of the cranial base is even less advanced, clinicians have noted [10]. This growth dysregulation at the cranial base is in part due to the absence of growth regulating genes for this area such as SHOX [12,13]. As a consequence, not only is the position of the external auditory meatus abnormal, giving the appearance of low set ears, but also the relationship of the middle ear to the Eustachian tube is disturbed. These factors, coupled with abnormalities in the shape of the palate, create a disposition to fluid collection and secondary infection. Among the most frequent craniofacial malformations, Gungor et al. [14] describe auricular prominence and a narrow and/or high arched palate as well as micrognathia. Marked hypocellularity of the mastoid air cells may also be found, further predisposing the individual to both acute and chronic suppurative disease [9,10,15,16]. In a careful study of immunological parameters in girls with TS no major immunological deficiency was found that could explain the increased incidence of OM in TS [17]. The parental origin of the intact X chromosome appears to influence the occurrence of otologic disease in TS [18].

The only study published, so far, on ear disease in very young girls is by Roush et al. [19]. Significant ear disease was present at study entry (mean age two years), with abnormal findings (one or both ears) by tympanometry in 63% and by hearing evaluation in 24%. Over the 2 years on study, GH-treated girls experienced slightly less otitis media ($9.4 \pm 12.2\%$ vs. $12.7 \pm 15.5\%$ of total days on study, based on reported adverse events) but the difference was not statistically significant. On-study rates of ME dysfunction (by tympanometry) did not

Table 1
Types of hearing loss in Turner syndrome (synoptical literature review)

Reference	Prevalence of ME disease (%)	Conductive HL (%)	Mixed HL (%)	SNHL (%)	SN configuration	Bilateral	Magnitude
Anderson et al. [9] (n=79)	52/76 (68)	8/79 (10)	9/79 (12)	51/79 (64)	33/79 mid-frequency dip (42%) 9/79 flat, sloping, high tone loss (11%)	22/33 9/79	20–70 dB (mean=35 dB)
Szpunar [16] (n=10)	7/10 (70)	5/18 (36)	13/18 (28)	0/18 (0)	6/18 mid-frequency dip (33%)	3/18	Mild 2/3 Moderate 1/3
Sculerati (1990) (n=22)	18/22 (82)	8/22 (36)	5/22 (23)	3/22 (14)		7/30	
Leheup (1988) (n=30)	51/60 (85)	14/30 (47)		7/30 (23)	4/7 mid-frequency dip (60%)	4/7	45 dB (mean=35 dB)
Watkin (1989) (n=24)	20/24 (83)		3/24 (12.5)	7/24 (30)	3/7 gently sloping from 4 kHz (40%) 3/7 gently sloping high tones loss (40%) 4/7 mid-frequency dip (60%)	3/7	
Hultcrantz (1994) (n=44)	23/44 (52)	0/44 (0)	5/44 (12)				
Sculerati [12] (n=24)	21/24 (87.5)	Unknown	4/24 (17)	16/24 (66)			
Güngör (2000) (n=38)	26/38 (68.4)	8/76 (10.5)	16/76 (21)	75/76 (98.7)	High-frequency hearing loss (6–18 kHz)		
Hultcrantz and Sylven [21] (n=44)	29/44 (67)		3/44 (7.5)	34/44 (77.5)	Mid-frequency dip 2-kHz dip (51.6%) 1.5-kHz dip (25.8%) 3-kHz dip (9.6%) 1-kHz dip (6.5%) 0.5-kHz dip (6.5%)	Bilateral	20 dB (younger group) 30.3 dB 50.6 dB
Ranke (2001)				50%	Mid-frequency (1–2 kHz dip)		

ME, middle ear; HL, hearing loss; SNHL, sensorineural hearing loss; HF, high frequency.

Table 2

Results of questionnaire asking for history of middle ear problems in Turner patients

Otologic history item	No. of patients (<i>n</i> =77) (%)
Recurrent or chronic middle ear disease	51 (66)
More than four episodes of otitis media annually	23 (45)
Previous myringotomy and/or tube placement	35 (45)
Tonsillectomy	34 (44)
Adenotomy	44 (56)
Major otologic surgery (tympanoplasty, tympanomastoidectomy)	10 (13)
ME problems at the time of the questionnaire	20 (25)
Tinnitus at present time	22 (28)
Regular attacks of vertigo at present time	7 (9)
Hearing aid at present time	6 (7)

ME, middle ear.

differ between control and GH-treated girls with abnormal hearing (29% → 12%) compared with control girls (19% → 21%) but the difference was not statistically significant.

3.2. Sensorineural hearing loss

SNHL is defined as elevated bone conduction threshold. When SNHL occurs it usually begins in late childhood or early adulthood and it is frequently gradually progressive. SNHL may occur without a history of severe chronic OM, and it may be absent, even with a history of severe chronic OM and multiple otologic procedures. Inner and middle ear diseases appear to be independent variables in TS. Audiologic investigations tend to identify the defect as one recruitment and specifically localized the defect to the outer hair cells of the organ of Corti [19]. The sensorineural hearing loss appears to develop with age and represent a degenerative rather than a congenital abnormality. Sensorineural hearing impairment is generally bilateral and characterized by symmetrical sensorineural dips in the mid-frequency range (in the 2 kHz region) in girls as young as 6 years [20] (Fig. 1A and B). Audiometric analysis showed further a conductive hearing loss (air–bone gap more than 10 dB HL). This degree of loss hardly causes any social hearing problems, since the dip is quite isolated and high and low frequency regions in hearing perception are preserved. When investigating the dip in Turner women aged 16–34 Hultcrantz and Sylven [21] found

Table 3

Middle ear findings in 41 Turner patients

Otologic diagnosis	No. of ears (<i>n</i> =87)
Marked tympanosclerosis	23
Perforation of the tympanic membrane	8
Retraction of the Sharpnell membrane	6
Incudostapedopexia of the tympanic membrane	5
Cholesteatoma	2
Middle ear effusion	3
Ventilation tube	3
Important atelectasis of the tympanic membrane	1

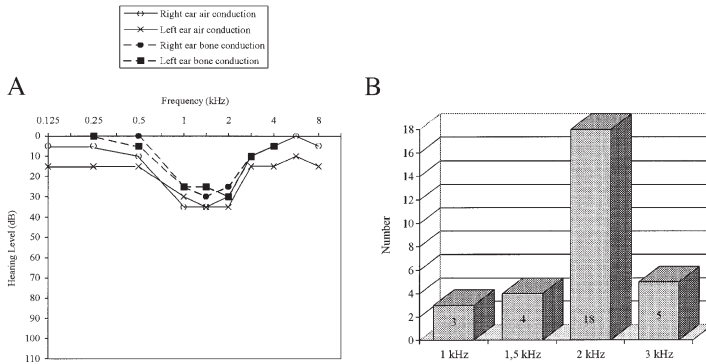


Fig. 1. (A) Audiogram showing the typical dip with the peak of 35 dB in the 1.5 kHz frequency region in a 12-year-old girl with Turner syndrome (karyotype 45,X). This girl has no subjective hearing problems. (B) Number of girls showing the sensorineural dip in different frequency regions. The dip is most common in the 2 kHz region.

a mean value of 30.3 dB HL and when looking at older women aged 39–69 the mean value had risen to 45.3 dB HL. The dip increases with age. In the older age group there is an early ageing of the ear, with a high-frequency loss added to the dip, leading to rapid onset of social hearing problems. If no dip is present, no hearing loss exceeding that of the normal ageing seems to be anticipated, which makes it possible to predict future hearing loss. 27% of the Swedish Turner women over 40 have hearing aids in comparison to 13% of children aged 0–8 in the normal population [22,23]. Stenberg et al. [20] stress that most of the young girls that present with a dip would not have been discovered in a regular screening test of 20 dB HL, as the peak of the dip did not exceed 20 dB HL and bone conduction is not always tested. Therefore both air and bone conduction have to be measured in order to discover the dip. A regular 20 dB HL screening test is simply not sufficient [20]. The detection of a high prevalence of high frequency hearing loss in young women with Turner syndrome (mean age 21 years) by Gungor et al. [14] brings a significant new perspective to otological disease in TS. High frequency audiometry (8–18 kHz) revealed sensorineural hearing loss in 98.7% of the ears. When hearing loss is detected with the conventional method, impairment of communication ability may have already occurred. Identification of initial hearing loss at frequencies above 8 kHz would provide warning before the hearing loss includes frequencies critical for verbal communication. The pathology seems to be a premature variant of presbycusis (normal aging decline of hearing) and it may underlie future hearing impairment. Thus Gungor [14] suggests it may be helpful to incorporate high frequency audiometric monitoring into conventional audiological testing in TS (Fig. 2).

The two karyotypes most frequently associated with a dip are 45,X and 45,X/46,X,i(Xq), 81.8% and 100%, respectively. These are among the most frequent karyotypes in TS. They demonstrate the most characteristic phenotype and have the greatest loss of X chromosome material. This makes it theoretically possible to predict future hearing problems [21]. Palatal dysfunction in these patients may be exacerbated by the removal of adenoids. Such surgery should be undertaken only after a careful evaluation of the patient’s speech and palatal configuration [24]. Estrogens may have a protective effect on hearing as

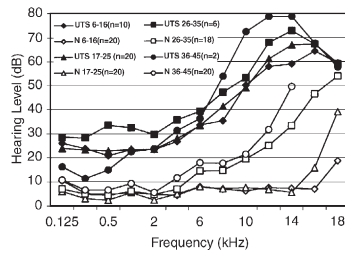


Fig. 2. Comparison of hearing levels of the study group with normal controls. As the higher frequencies are approached, the measurement limits for hearing level in the audiometer fall under 70 dB. Thus, the numerical values for hearing levels within the whole spectrum of the HF audiometry are not included. (N =normal controls).

older women hear slightly better than men [25,26]. Estrogens may therefore have a certain protective effect on hearing. Studies of estrogen receptors in man and in Turner mouse model have so far been inconclusive [27]. In a turner mouse model, auditory brain stem responses showed a progressive hearing loss in the high frequency region that exceeded the normal age-related hearing loss. Outer hair cell loss was apparent in the cochlea. These results indicate that hearing problems in the Turner mouse seems to be of cochlear origin with an eighth nerve component [28]. In the clinical setting current regimens of estrogen and GH therapy had no impact on adult hearing loss in TS, independent of age [29]. Based on present evidence the only possible intervention to reduce hearing loss in women with TS remains assiduous treatment of all ENT problems in childhood.

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